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Epidemiology of multiple sclerosis in western Herzegovina

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Abstract

Objectives: To determine epidemiological rates of multiple sclerosis (MS) in western Herzegovina.
Patients and methods: We analysed data from 81 MS patients (49 females, 32 males) on the prevalence day, 31 December 2003. Patient information was obtained from a search of all available medical records from the period 1994–2003 in the investigated area.
Results: Crude prevalence of MS was 27/100,000 (95% confidence interval (CI) 20–34). Prevalence was highest in the mountainous municipality of Posušje (56/100,000) and lowest in the coastal municipality of Neum (0 incidence). The annual incidence of MS was 1.6/100,000 (95% CI 0–3.3). The female/male ratio of MS was 1.5. The mean age of the patients on prevalence day was 40.0 ± 11.6 years, and the mean age at disease onset was 31.0 ± 7.1 years. Eight (10%) of the patients had a first-degree relative with MS. The primary progressive (PP) disease course was observed only in females. Visual symptoms were the initial symptom of MS in 6 (7%) of the patients.
Conclusions: Western Herzegovina is an area of moderate risk for MS, and the distribution of MS in western Herzegovina is heterogeneous. PP-MS occurred only in females, and involvement of the visual pathways as the initial symptom of MS was low.

Keywords: Multiple sclerosis; Prevalence; Incidence; Herzegovina; Europe

1. Introduction

Recent epidemiological reports of multiple sclerosis (MS) in Europe include all of the former Yugoslavian republics, with the exception of Bosnia and Herzegovina (BH) [1,2]. Here, we present descriptive epidemiological data regarding MS in western Herzegovina.

2. Methods

2.1. Study area

The study area, Herzegovinian-Neretvan and western Herzegovina counties, occupies the southwestern part of BH, 42°53′–43°39′ latitude and 17°19–17°58′ longitude (Fig. 1). The 5763 km^2 area is divided into a high-karst zone, up to 1000 m above sea level; a moderate continental climate zone, with abundant precipitation; and a Mediterranean zone. Flora is subtropical. Fauna are comprised of Mediterranean and karst species. In mountainous areas, cattle farming is

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Fig. 1. Location of western Herzegovina.

a dominant economic feature, while tobacco-, grape- and vegetable-farming predominates in coastal regions. Significant deposits of bauxite have fostered the aluminium industry.

Low birth-rate and emigration hinder population growth in western Herzegovina. Primary health care is organized in all municipalities, and neurological services are provided by the university hospital and regional medical centre in Mostar and by the general hospital in Konjic. The population is Illyrian, with a presence of ancient Italic in settlements along the main roads. During Turkish rule (1463–1878), the area was known as Herzegovinian Sandžak and was renamed Herzegovina during the Austrian–Hungarian Empire (1878–1918). Herzegovina is the name used by all subsequent regimes of the South Slavs. On 31 December 2003, 300,746 persons were living in the study area (162,057 females and 138,689 males), including Croats (64%), Bosnians (34%), and Serbs (2%) [3–5].

2.2. Patients

The restrospective study included patient information collected from 1 January 1994 to 31 December 2003. MS patients were identified from the archives of the Department of Neurology of the university hospital, the Department of Neurology and Psychiatry of the regional medical centre in Mostar, the Department of Neurology and the neurological outpatient services of the general hospital in Konjic, and the medical records of the neurological outpatient services in Jablanica, Čapljina, Čitluk, Ljubuški, Široki Brijeg, Grude, Posušje, Prozor-Rama, Neum, and Stolac. Diagnosis was confirmed with magnetic resonance (MR) images of the brain and cervical spine of all patients. In 75 (92%) of the cases MR imaging (MRI) was performed two or more times. Cerebrospinal fluid (CSF) was obtained by lumbar puncture in 72 (89%) patients for comparison with matched serum. Each CSF sample was analysed for cell counts, glucose, albumin, immunoglobulin G (IgG), and oligoclonal IgG banding. Evoked potentials were tested in 42 (51%) patients. Additional examinations and analyses were performed as necessary, including cardiologic examination with echocardiography and assessment of antinuclear antibodies; coagulation; syphilitic serology; *B. burgdorferi*-specific antibody index; neurotropic virus serology, including human immunodeficiency virus (HIV), human herpes virus-6 (HHV-6), herpes simplex virus (HSV), Epstein-Barr virus (EBV); and brucellosis serology. In four female primary progressive (PP)-MS patients, plasma with very long chain fatty acids was analysed. The research was perfomed with the approval of the Croatian Medical Association Ethical Committee. Data for each patient were collected and stored in the EDMUS data base (version 3.4) [6]. MS cases were considered prevalent according to McDonald et al. [7]. The date of MS onset, defined as the time of the first neurological symptom attributable to the disease, was provided by patients or medical records [8]. MS was categorised as relapsing-remitting (RR)-MS, PP-MS, or secondary progressive (SP)-MS [9]. Patients were deemed prevalent if they were living in the study area on the prevalence day, 31 December 2003. The incidence of MS within families was considered only in first-degree relatives (i.e., parents, children, siblings).

2.3. Statistical analysis

Statistical analysis was performed using Statistica software package version 7.0 and Computer Programs for Epidemiologic Analyses PEPI version 4.0. Quantitative vari-

Table 1
Selection of 81 western Herzegovina multiple sclerosis study patients from 122 potential cases on 31 December 2003

Potential cases	Present on prevalence day	102
	Emigrated	4
	Died	6
Excluded cases	Other neurological diseases	8
	Did not satisfy criteria	3
Accepted patients		81

ables were characterised as means and standard deviations. Nominal variables were characterised as absolute and relative frequencies. Crude prevalence and incidence rates were calculated. Rate standardisation was performed with the direct standardisation method applied to the study area population to allow international comparison with a "new" European population [10,11]. Statistical differences were tested with Chi-square tests. *P*-values <0.05 were considered to be statistically significant. Ninety-five percent confidence intervals (95% CIs) were based on an assumed Poisson distribution. Between-group differences were tested with *t*-tests.

3. Results

Data for 102 potential MS patients identified between 1 January 1994 and 31 December 2003 were combined (Table 1). Eighty-one MS patients, including 49 (60%) females and 32 (40%) males, were considered to be prevalent cases, according to the diagnostic criteria of McDonald et al. [7]. For eight patients, a previous diagnosis of MS was rejected. Three of those patients had cerebrovascular disease, two had a dissociated movement and sensation disorder, one had viral encephalomyelitis, one had a spinal tumour, and one had familiar spastic paraplegia.

Crude prevalence of MS in western Herzegovina on 31 December 2003 was 27/100,000 (95% CI 20–34) (Table 2). The crude prevalence of MS was 30/100,000 (95% CI 20–40) for females and 23/100,000 (95% CI 14–33) for males. MS prevalence did not differ between males and females ($P = 0.23$). None of the patients was younger than 15 years.

Table 2
Prevalence[a] of multiple sclerosis in western Herzegovina, by age and sex on 31 December 2003

Age (years)	Males		Females		Total		95% confidence interval
	N	Rate	*N*	Rate	*N*	Rate	
<15	–	–	–	–	–	–	–
16–64	30	31.6	48	42.2	78	37.4	
>65	2	12.2	1	4.4	3	7.7	
	32		49		81	26.9	19.9–33.9
Age adjusted[b]						26.09	

[a] Per 100,000.
[b] According to European population standard.

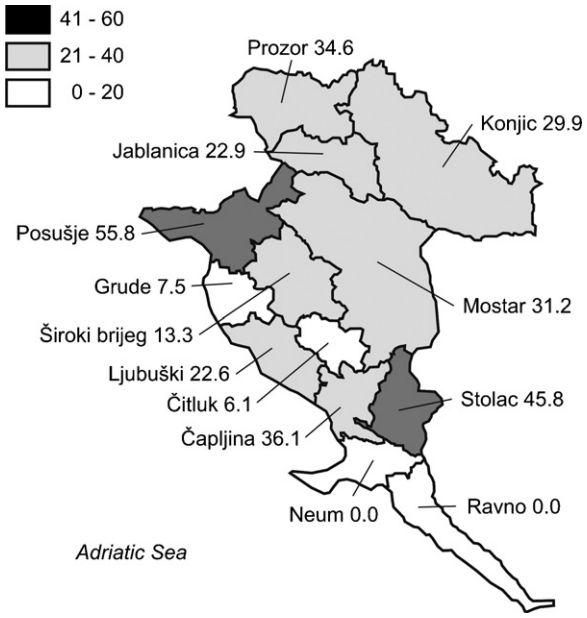

Fig. 2. Prevalence of multiple sclerosis (per 100,000 inhabitants) in western Herzegovina municipalities on 31 December 2003.

The distribution of MS in western Herzegovina was heterogeneous (Fig. 2). The prevalence of MS was highest in the municipalities of Posušje (56/100,000; 95% CI 13–99) and Stolac (46/100,000; 95% CI 0–94). None of the patients were living in the municipalities of Neum or Ravno on prevalence day.

The average annual incidence of MS between 1 January 1994 and 31 December 2003 was 1.6/100,000 (95% CI 0–3.3) (Fig. 3). The incidence rate in 1994–1998 was 1.6/100,000/year (95% CI 0–3.3), which did not differ significantly from the incidence rate in 1999–2003 (1.7/100,000/year; 95% CI 0–3.4). The highest incidence was 2.7/100,000 in 1998, which represents a 5-fold increase over the 1994 incidence of 0.6/100,000. The mean age of prevalent cases was 40 ± 12 years (range 17–67; 40 ± 12 years, range 17–67 for males; 41 ± 12 years, range 21–65 for females). The mean age at onset was 31 ± 7 years (range 17–47 years;

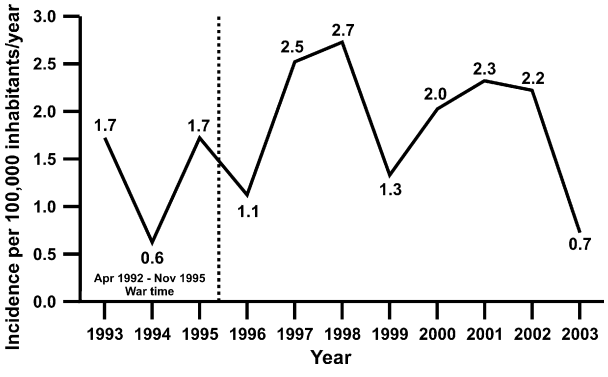

Fig. 3. Annual incidence of multiple sclerosis in western Herzegovina from 1994 to 2003.

30 ± 7 years for males and 31 ± 7 years for females). The average duration of the disease from onset to prevalence day was 9 ± 9 years (range 1–34 years; 10 ± 7 years for males and 9 ± 8 years for females).

The disease was categorised as RR-MS in 45 (56%) patients, SP-MS in 29 (36%) patients, PP-MS in 6 (7%) patients, and PR-MS in 1 (1%) patient. The PP-MS and PR-MS patients were female. The frequency of RR-MS and SP-MS was not significantly different in males and females ($P = 0.82$).

Eight patients (10%) had a history of MS among first-degree relatives. In one family monozygotic twin sisters contracted the disease within 2 years of each other (one at age 27 and one at age 29) during puerperium.

Initial symptoms were established in all patients. Thirty-two percent of the patients had initial motor symptoms, 41% had sensory symptoms, 11% had brainstem symptoms, 10% had vestibulocerebellar symptoms, and 7% had visual symptoms. Twenty-seven (33%) patients had more than one initial symptom.

4. Discussion

Zec [12] was the first to attempt to characterise the distribution of MS in BH. Based on analysis of the medical records of 202 inpatients, he concluded that "0.5–1‰ of inhabitants of the Sarajevo region have MS, and the disease is more frequent in the north-western than in the south-eastern areas of the country." He goes on to explain the geographical distribution: "MS is more frequent in areas which were the pathways of invasions through the centuries. "Following this pioneering research, there were other scarce and methodologically flawed investigations. Sulejmanović et al. [13] analysed medical records from 1982 to 1987 and reported that the annual incidence of MS was 2.3/100,000 in the Tuzla municipality and 1.3/100,000 in the Tuzla district. The prevalence of MS in the Tuzla region (i.e., northeastern Bosnia) on 31 March 1981 was 8/100,000.

Đelilović-Vranić et al. [14] recently confirmed a greater frequency of MS in post-war Sarajevo, with 107 patients (64% female, 36% male) in 1996–2000 compared to 72 patients (36% female, 64% male) in 1986–1995. The inversion of MS incidence in males and females illustrates the phenomenon that females are more sensitive to MS during severe environmental (i.e., wartime) conditions. On the basis of information from the Association of MS Patients in the Republic of Srpska, the prevalence of MS was assessed at 17/100,000 (S. Grgić, MD, oral communication, February 2007). The small investigated area, with branched neurological service; the possibility of clinical treatment of patients *in loco* and abroad; and a carefully planned epidemiological study of MS in a population that was sensitised by a preliminary study [15] enabled evaluation of a nearly complete sample of MS patients. An MS diagnosis was incorrect in 8% of cases evaluated.

A crude prevalence of 27/100,000 and an average annual incidence of 1.6/100,000 places western Herzegovina in a zone of moderate MS risk. This prevalence rate is higher than the estimated 16/100,000 for the same area in 2002 [15]. The bordering regions of Croatia, which were investigated using the same methodology but applying Poser's diagnostic criteria for clinically definite MS [16] show similar parameters. Dubrovnik-Neretva county has an MS prevalence of 24/100,000 and an annual incidence of 2.2/100,000. The prevalence rate for Šibenik-Knin county is 30/100,000, and the prevalence rate for Zadar county is 31/100,000. Zadar county has an annual incidence of 2.8/100,000 [17]. Continental, mountainous municipalities (i.e., Posušje, Stolac), which have a cold climate and greater amounts of winter precipitation, have a higher prevalence of MS than coastal municipalities (i.e., Neum, Ravno), which have warm climates and a high number of sunny days. There were no documented cases of MS in Neum and Ravno municipalities during the study period. Variations in the MS distribution in small geographical areas have been observed elsewhere in southeastern Europe [18,19]. The heterogeneous distribution of MS in western Herzegovina is a consequence of the recent war (April 1992–November 1995). The entire area, especially the municipalities of Mostar, Čapljina, and Stolac, were the scenes of turbulent events. In our opinion, the lower incidence of MS in the investigated area during the war was due to increased emigration, the collapse of health services, and the primary concern of residents regarding their health. The incidence of MS increased during the post-war period. The introduction of MRI for the diagnosis of MS is not likely to be the only factor responsible for the increase, as neuroimaging techniques have been used in the investigated area since the 1990s. The higher prevalence of MS in females and the average age at MS onset obtained in the present study are consistent with similar studies across the world [20,21].

Compared to other European studies, our results indicated a lower average age of MS patients and a shorter average duration of the disease on prevalence day. This is indicative of adverse living conditions in the study area, particularly during the last decade. In western Herzegovina, MS patients rarely live beyond 60 years of age. Some clinical characteristics of MS patients included in the present study deserve comment. For instance, optical neuritis was less frequently an initial symptom of MS in our patients compared to those evaluated in classic studies [20,22]. Furthermore, contrary to observations by Cottrell et al. [23], PP-MS was diagnosed only in females in the present study. The prevalence of MS in females, the shorter duration of life for males in the investigated area, and the small sample of MS patients may partially explain this finding. The frequency of first-degree relatives with MS in the present study is lower than reported for most populations [24,25].

In conclusion, our retrospective, epidemiological study is the first to be conducted in BH, based on generally accepted methodological principles and present-day MS

diagnostic criteria. Our results indicate that within south-east Europe, western Herzegovina is an area of moderate risk for MS.

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